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PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : C07D 263/32, 413/10, A61K 31/42 | A1 | (11) International Publication Number: WO 98/55468 (43) International Publication Date: 10 December 1998 (10.12.98) |
| (21) International Application Number: PCT/JP98/02398 (22) International Filing Date: 1 June 1998 (01.06.98) (30) Priority Data: PO 7132 2 June 1997 (02.06.97) AU (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): HATTORI, Kouji [JP/JP]; 1-7-1-915, Sumiregaoka, Takarazuka-shi, Hyogo 665-0847 (JP). OKITSU, Osamu [JP/JP]; 57-2A, Minamienoki-cho, Shinjuku-ku, Tokyo 162-0852 (JP). FUJII, Naoaki [JP/JP]; 15-1-221, Tonomachi, Takatsuki-shi, Osaka 569-1126 (JP). TANAKA, Akira [JP/JP]; 9-10-302, Nakano-cho, Takarazuka-shi, Hyogo 665-0056 (JP). TANIGUCHI, Kiyoshi [JP/JP]; 2-1-28, Minamiochiai, Suma-ku, Kobe-shi, Hyogo 654-0153 (JP). KOYAMA, Satoshi [JP/JP]; 6-10-22, Kitatomigaoka, Nara-shi, Nara 631-0001 (JP). NISHIO, Mie [JP/JP]; 98-3, Houjiyo Umeharacho, Himeji-shi, Hyogo 670-0945 (JP). | (74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP). (81) Designated States: BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. | |
| (54) Title: OXAZOLE COMPOUNDS USEFUL AS PGE2 AGONISTS AND ANTAGONISTS | | |
| (57) Abstract | | |
| <p>Azole compounds of formula (I) wherein R¹ is lower alkyl substituted with carboxy, etc., R² is hydrogen or lower alkyl, R³ is aryl, etc., R⁴ is aryl, etc., Q is formula (a), etc., and X is O, NH or S, and its salts, which are useful as medicament.</p> | | |
| <div style="text-align: center;"> </div> <div style="text-align: right;">(I)</div> | | |
| <div style="text-align: center;"> </div> <div style="text-align: right;">(a)</div> | | |

DESCRIPTION

OXAZOLE COMPOUNDS USEFUL AS PGE₂ AGONISTS AND ANTAGONISTS5 TECHNICAL FIELD

This invention relates to azole compounds and its salts which are useful as a medicament.

BACKGROUND ART

10 Some azole compounds are known, for example, in WO 95/17393, WO 95/24393 and WO 97/03973.

DISCLOSURE OF INVENTION

15 This invention relates to azole compounds. More particularly, this invention relates to azole compounds and its salts which are useful as prostaglandin E₂ (hereinafter described as PGE₂) agonist or antagonists.

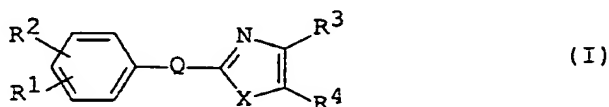
Accordingly, one object of this invention is to provide new and useful azole compounds and its salts.

20 Another object of this invention is to provide processes for production of the azole compounds or its salts.

A further object of this invention is to provide a pharmaceutical composition containing, as an active ingredient, said azole compounds or its salts.

25 Still further object of this invention is to provide use of the azole compounds and its salts for manufacture of medicaments for treating or preventing PGE₂ mediated diseases.

30 The azole compounds of this invention can be represented by the following formula (I) :



35 wherein R¹ is lower alkyl substituted with hydroxy, protected

PGE₂ is known as one of the metabolites in an arachidonate cascade. And it is also known that it has various activities such as pain inducing activity, inflammatory activity, uterine contractile activity, a
5 promoting effect on digestive peristalsis, an awakening activity, a suppressive effect on gastric acid secretion, hypotensive activity, blood platelet inhibition activity, bone-resorbing activity, angiogenic activity, or the like.

PGE₂-sensitive receptors have been sub-divided into four
10 subtypes, EP1, EP2, EP3 and EP4, and these receptors have a wide distribution in various tissues. The effects associated with EP1 and EP3 receptors may be considered as excitatory, and are believed to be mediated by stimulation of phosphatidylinositol turnover or inhibition of adenylyl cyclase
15 activity, with resulting decrease in intracellular levels of cyclic AMP. In contrast, the effects associated with EP2 and EP4 receptors may be considered as inhibitory, and are believed to be associated with a stimulation of adenylyl cyclase and an increase in levels of intracellular cyclic
20 AMP. Especially, EP4 receptor may be considered to be associated with smooth muscle relaxation, anti-inflammatory or pro-inflammatory activities, lymphocyte differentiation, antiallergic activities, mesangial cell relaxation or proliferation, gastric or enteric mucus secretion, or the
25 like.

The azole compounds represented by the formula (I) or its salts possess binding activities to PGE₂-sensitive receptors, specifically to EP4 receptor, therefore they possess a PGE₂-antagonizing or PGE₂-inhibiting activity.

30 Therefore, the compounds represented by the formula (I) or its salts are useful for preventing or treating a PGE₂ mediated diseases, especially a EP4 receptors-mediated diseases, such as inflammatory conditions, various pains, or the like in human beings or animals.

35 More particularly, the compounds represented by formula

(I) and its salt are useful for treating or preventing inflammation and pain in joint and muscle (e.g., rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.), inflammatory skin condition (e.g., sunburn, burns, eczema, dermatitis, etc.), inflammatory eye condition (e.g., conjunctivitis, etc.), lung disorder in which inflammation is involved (e.g., asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.), condition of the gastrointestinal tract associated with inflammation (e.g., aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.), gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, allergic disease, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjögren's syndrome, Behcet disease, thyroiditis, type I diabetes, diabetic complication (diabetic microangiopathy, diabetic retinopathy, diabetic neohropathy, etc.), nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, kidney dysfunction (nephritis, nephritic syndrome, etc), liver dysfunction (hepatitis, cirrhosis, etc.), gastrointestinal dysfunction (diarrhea, inflammatory bowel diseases, etc.) shock, bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, cancer cachexia, calculosis, lithiasis (especially, urolithiasis), solid caricinoma, or the like in human being or animal.

In order to show the utility of the object compound (I), pharmacological data of the representative compounds thereof are shown in the following.

5 Binding assay using expression of prostanoid receptor
 subtype

[I] Test Compound :

- 10 (1) (S)-2-(4,5-Diphenyloxazol-2-yl)-1-(3-methoxybenzyl)-2-cyclopentene
- (2) (S)-4-([2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl)benzoic acid
- 15 (3) (S)-{3-([2-(4,5-Diphenyloxazol-2-yl)-2-cyclohexen-1-yl]-methyl)phenoxy}actamide

[II] Test Method :

20

The membrane fraction was prepared using COS-7 cells transfected prostanoid receptor subtype (human EP4).

25 The Standard assay mixture contained membrane fraction, [³H]-PGE₂ in final volume of 0.25 ml was incubated for 1 hour at 30°C. The reaction was terminated by that the mixture was rapidly filtered through a glass filter (GF/B). Then the filter was washed by 4 ml of ice-cold buffer at two times. The radioactivity associated with the filter was measured by liquid scintillation counting.

30 In the experiment for competition of specific [³H]-PGE₂ was added at a concentration of 10 μM. The following buffer was used in all reactions.

 Buffer: 20mM Mes (pH 6.0), 1mM EDTA, 10mM MgCl₂

35 The inhibition (%) of each compound at a concentration of 10 μM was shown in Table.

[III] Test Result :

| Test Compound | | Inhibition(%) |
|---------------|--------------|---------------|
| (1) | (10 μ M) | >80 |
| (2) | (10 μ M) | >80 |
| (3) | (10 μ M) | >80 |

Effect on IgE and IgG₁ secretion in mouse B lymphocytes

[I] Test Compound

Sodium (S)-3-([2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl)benzoate

[II] Test Method

Inhibitory properties of a test compound against PGE₂-induced IgE and IgG₁ secretion in isolated resting B lymphocytes of mice were tested. Resting mouse B lymphocytes were isolated from spleens of 12-week-old BDF₁ male mice (Clea Japan Inc.) using adherent cell depletion, negative selection by FITC-anti-Thy 1.2 (30H12), FITC-anti-CD4 (GK1.5), FITC-anti-CD11b (M1/70) and FITC-anti-CD8a (5.-6.7) (Pharmingen) with anti-FITC Ab coating magnetic beads (Perspective Daiagnostics) and Percoll gradient (Pharmacia). Resting B lymphocytes were cultured in flat-bottomed 96-well microtiter plates (Becton Dickinson) at 1 x 10⁶ cells per ml and preincubated with a test compound or DMSO control for 30 minutes. Then PGE₂ were added at 10⁻⁶ M. After 1 hour, LPS and IL-4 were added and incubated at 37°C in a humidified atmosphere with 5% CO₂. After 6 days, supernatants were collected and IgE and IgG₁ were measured by the ELISA.

[III] Test Result

| | -PGE ₂ | + 10 ⁻⁶ M PGE ₂ |
|-------------------------------------|-------------------|---------------------------------------|
| IgE secretion (ng/ml) | | |
| Control | 27.6 ± 9.9 | 136.9 ± 22.2 # |
| + 10 ⁻⁵ M Test Compound | 21.2 ± 5.7 | 37.0 ± 7.0 * |
| IgG ₁ secretion (ng./ml) | | |
| Control | 680.1 ± 37.9 | 1970.7 ± 117.5 # |
| + 10 ⁻⁵ M Test Compound | 1053.0 ± 176.2 | 1607.6 ± 150.9 # |

Data : Mean ± S.E.M. (n = 4)

p<0.01 v.s. Control (-PGE₂)

* p<0.01 v.s. Control (+ 10⁻⁶ M PGE₂) (Dunnett)

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form (e.g., tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, solution, emulsion, suspension etc.), which contains the object compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g., sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agent (e.g., cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g., starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch,

sodium glycol-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g., magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g., citric acid, mentol, glycine, orange powders, etc.),
5 preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g., citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g., methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent
10 (e.g., water), base wax (e.g., cacao butter, polyethyleneglycol, white petrolatum, etc.).

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 50 mg/kg, 1 to 4 times a
15 day. However, the above dosage may be increased or decreased according to age, weight, conditions of the patient or the administering method.

The patents, patent applications and publications cited
20 herein are incorporated by reference.

Abbreviations used in this application are as follows :

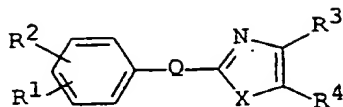
| | | | |
|----|--------------------|---|--------------------------|
| | THF | : | Tetrahydrofuran |
| | EtOAc | : | Ethyl acetate |
| 25 | Et ₂ O | : | Diethyl ether |
| | DMF | : | N,N-Dimethylformamide |
| | EtOH | : | Ethyl alcohol |
| | MeOH | : | Methyl alcohol |
| | AcOH | : | Acetic acid |
| 30 | nBuli | : | n-Butyllithium |
| | MsCl | : | Methanesulfonyl chloride |
| | pTsOH | : | p-Toluenesulfonic acid |
| | AcONH ₄ | : | Ammonium acetate |
| | DMAP | : | Dimethylaminopyridine |
| 35 | Pd/C | : | Palladium on carbone |

$\text{Pd(OH)}_2/\text{C}$: Palladium hydroxide on carbone

The following Preparations and Examples are given only
for the purpose of illustrating the present invention in more
5 detail.

C L A I M S

1. A compound of the formula :



wherein

- 10 R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; halo(lower)alkylsulfonyloxy; lower alkoxy substituted with hydroxy or carbamoyl; aryl
- 15 substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,
- R^2 is hydrogen or lower alkyl,
- 20 R^3 is aryl optionally substituted with halogen,
- R^4 is aryl optionally substituted with halogen,
- Q is $-A^1-\text{A}_2-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, A_2 is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or bicyclo(C_5-C_9)alkane, and $-A^3-$ is a single bond or lower alkylene], and
- 25 X is O, NH or S, and its salt.

30

2. A compound according to the claim 1, wherein X is O.

3. A compound according to the claim 2, wherein

35 R^1 is lower alkyl substituted with carboxy; carboxy;

protected carboxy; carbamoyl; a heterocyclic group;
lower alkoxy substituted with carbamoyl; aryl
substituted with carboxy, carbamoyl or a
heterocyclic group; or amino optionally substituted
with lower alkylsulfonyl.

5

4. A compound according to the claim 3, wherein

R^1 is lower alkyl substituted with carboxy; carboxy;
carbamoyl; tetrazolyl; lower alkoxy substituted
with carbamoyl; aryl substituted with carboxy or
carbamoyl, and

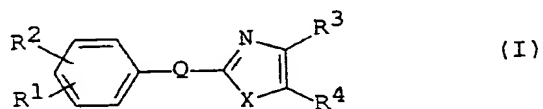
10

Q is $-A^1-\textcircled{A_2}-A^3-$ (in which $-A^1-$ is methylene, $\textcircled{A_2}$ is
cyclo(C_5-C_7)alkene, cyclo(C_5-C_7)alkane,
bicyclo[2.2.1]heptene or bicyclo[2.2.1]heptane, and
 $-A^3-$ is a single bond).

15

5. A process for production of the compound of the
formula :

20



wherein

25

R^1 is lower alkyl substituted with hydroxy, protected
carboxy or carboxy; carboxy; protected carboxy;
carbamoyl; a heterocyclic group; cyano;
halo(lower)alkylsulfonyloxy; lower alkoxy
substituted with hydroxy or carbamoyl; aryl
substituted with carboxy, protected carboxy,
carbamoyl or a heterocyclic group; or amino
optionally substituted with protected carboxy or
lower alkylsulfonyl,

30

R^2 is hydrogen or lower alkyl,

35

R^3 is aryl optionally substituted with halogen,

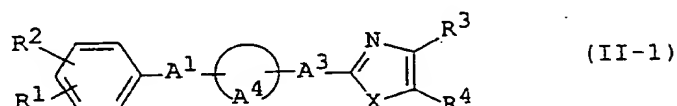
R^4 is aryl optionally substituted with halogen,

Q is $-A^1-\textcircled{A_2}-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, $\textcircled{A_2}$ is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or bicyclo(C_5-C_9)alkane, and $-A^3-$ is a single bond or lower alkylene], and

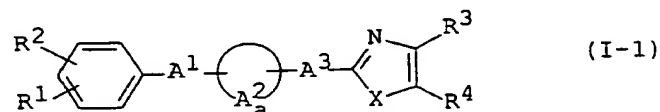
X is O, NH or S,

or its salt, which comprises,

(1) dehydrating a compound of the formula :



or its salt, to give a compound of the formula :



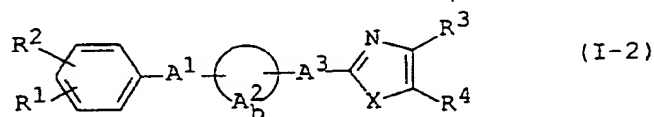
or its salt, in the above formulas,

R^1 , R^2 , R^3 , R^4 , $-A^1-$, $-A^3-$ and X are each as defined above,

$\textcircled{A_{2a}}$ is cyclo(C_5-C_9)alkene or bicyclo(C_6-C_9)alkene, and,

$\textcircled{A_4}$ is cyclo(C_5-C_9)alkane or bicyclo(C_6-C_9)alkane, each of which is substituted with hydroxy,

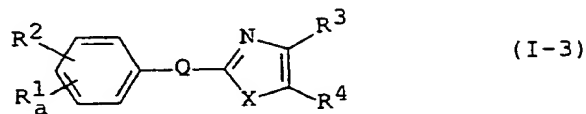
(2) reducing the compound of the formula (I-1) defined above, or its salt, to give a compound of the formula :



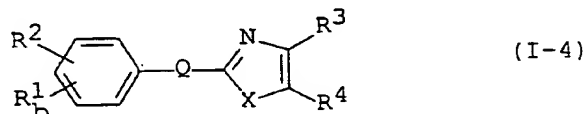
or its salt, in the above formula, R^1 , R^2 , R^3 , R^4 , $-A^1-$, $-A^3-$ and X are each as defined above, and

A_2 is cyclo(C₅-C₉)alkane or bicyclo(C₆-C₉)alkane,

(3) subjecting a compound of the formula :

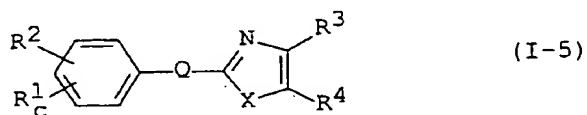


or its salt, to (a) a cleavage of ether bond and
(b) a halo(lower)alkylsulfonylation, to give a
compound of the formula :



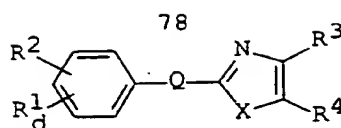
or its salt, in the above formulas,
R², R³, R⁴, Q and X are each as defined above,
R^{1a} is lower alkoxy, and
R^{1b} is halo(lower)alkylsulfonyloxy,

(4) subjecting the compound of the formula (I-4)
defined above, or its salt, to Pd-catalyzed
carbonylation, to give a compound of the formula :



or its salt, in the above formula,
R², R³, R⁴, Q and X are each as defined above, and
R^{1c} is protected carboxy,

(5) subjecting the compound of the formula (I-5)
defined above, or its salt, to deesterification, to
give a compound of the formula :



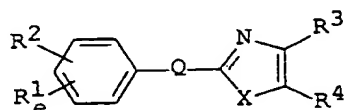
(I-6)

or its salt, in the above formula,
 R^2 , R^3 , R^4 , Q and X are each as defined above, and
 R_{d}^1 is carboxy,

- (6) reacting the compound of the formula (I-6) defined above, or its reactive derivative at the carboxy group, or its salt, with a compound of the formula :



or its reactive derivative, or its salt, to give a compound of the formula :

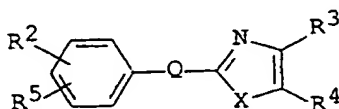


(I-7)

or its salt, in the above formulas,
 R^2 , R^3 , R^4 , Q and X are each as defined above, and
 R_e^1 is carbamoyl.

- (7) reacting the compound of the formula (I-5) defined above, or its salt, with the compound of the formula (III) defined above, or its salt, to give the compound of the formula (I-7) or its salt, or,

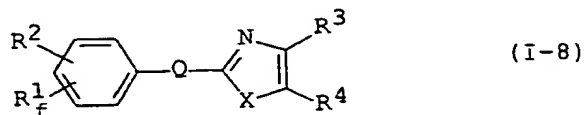
- (8) reacting a compound of the formula :



(II-2)

or its reactive derivative at carboxy group, or its salt, with the compound of the formula (III)

defined above, or its reactive derivative, or its salt, to give a compound of the formula :



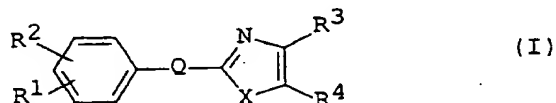
or its salt, in the above formula,

R^2 , R^3 , R^4 , Q and X are each as defined above,

R^1 is lower alkoxy substituted with carbamoyl, and

R^5 is lower alkoxy substituted with carboxy or protected carboxy.

6. A Pharmaceutical composition containing a compound of the formula :



wherein

R^1 is lower alkyl substituted with hydroxy, protected carboxy or carboxy; carboxy; protected carboxy; carbamoyl; a heterocyclic group; cyano; hydroxy; halo(lower)alkylsulfonyloxy; lower alkoxy optionally substituted with hydroxy or carbamoyl; aryl substituted with carboxy, protected carboxy, carbamoyl or a heterocyclic group; or amino optionally substituted with protected carboxy or lower alkylsulfonyl,

R^2 is hydrogen or lower alkyl,

R^3 is aryl optionally substituted with halogen,

R^4 is aryl optionally substituted with halogen,

Q is $-A^1-\text{A}_2-A^3-$ [in which $-A^1-$ is a single bond or lower alkylene, A_2 is cyclo(C_5-C_9)alkene, cyclo(C_3-C_9)alkane, bicyclo(C_6-C_9)alkene or

bicyclo(C₅-C₉)alkane, and -A³- is a single bond or lower alkylene], and

X is O, NH or S,

or its salt, as an active ingredient, in association
5 with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A use of the compound of claim 6 as a medicament.

10 8. A use of the compound of claim 6 as an agonist or an antagonist of PGE₂-sensitive receptor.

9. A method for treating or preventing PGE₂ mediated diseases which comprises administering an effective
15 amount of a compound of claim 6 to human beings or animals.

10. The method for treating or preventing inflammatory conditions, various pains, collagen diseases, autoimmune
20 diseases, various immunity diseases, analgesic, thrombosis, allergic disease, cancer or neurodegenerative diseases which comprises administering an effective amount of a compound of claim 6 to human beings or animals.

25 11. A use of a compound of claim 6 for the manufacture of a medicament for treating or preventing PGE₂ mediated diseases in human beings or animals.

30

35

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 98/02398

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D263/32 C07D413/10 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 97 03973 A (FUJISAWA PHARMACEUTICAL CO ; TANIGUCHI KIYOSHI (JP); HATTORI KOUJI) 6 February 1997 cited in the application see claims 1-5, 10-14; examples 32, 34 | 1-11 |
| X | WO 95 17393 A (FUJISAWA PHARMACEUTICAL CO ; TANIGUCHI KIYOSHI (JP); NAGANO MASANOBU) 29 June 1995 cited in the application see the whole document | 1-11 |
| A | US 5 100 889 A (MISRA RAJ N ET AL) 31 March 1992 see the whole document | 1-11 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

20 August 1998

Date of mailing of the international search report

31/08/1998

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INTERNATIONAL SEARCH REPORT

I. International application No.

PCT/JP 98/02398

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9 and 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9 and 10
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 98/02398

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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